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Association of serum chloride levels with all-cause mortality among patients in surgical intensive care units: a retrospective analysis of the MIMIC-IV database

Quan Ma[1], Wei Tian[1], Kaifeng Wang[1], Bin Xu[2] and Tianyu Lou[3*]

Abstract

This study explores the association between serum chloride concentrations and all-cause mortality among patients in the Surgical Intensive Care Unit (SICU). Employing a retrospective cohort design, the study utilized data extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, specifically focusing on individuals admitted to the surgical/trauma ICUs. This dataset encompassed demographic profiles, laboratory findings, historical medical data, vital statistics, and variables pertinent to prognosis. Participants were divided into four groups based on their serum chloride concentrations. The primary outcomes assessed were mortality rates at 30, 90, and 180 days post-admission to the ICU. Analytical methods included Kaplan–Meier survival curves, Cox proportional hazards regression models, and Restricted Cubic Spline (RCS) analyses to delineate the relationship between serum chloride concentrations and patient outcomes. The study cohort comprised 10,996 patients, with observed mortality rates of 12.78% at 30 days, 17.14% at 90 days, and 20.32% at 180 days. Kaplan–Meier analyses revealed significant disparities in survival rates across the quartiles of serum chloride during the follow-up intervals ($p < 0.001$). The results from the multivariable Cox regression suggested a substantial inverse association between high serum chloride levels and decreased mortality at 30 days (hazard ratio [HR]: 0.96; 95%confidence interval [CI]: 0.95–0.97; $P < 0.001$), 90 days (HR: 0.97; 95% CI: 0.96–0.98; $P < 0.001$), and 180 days (HR: 0.97; 95% CI: 0.96–0.98; $P < 0.001$). Particularly, patients in the highest quartile of serum chloride faced significantly lower mortality risks compared to those in the lowest quartile (30 days HR = 0.65, 90 days HR = 0.71, 180 days HR = 0.69, $P < 0.001$). RCS analysis depicted an L-shaped curve demonstrating the dynamics between serum chloride concentrations and the risk of all-cause mortality across the 30-day, 90-day, and 180-day periods.Starting at a concentration of 104 mmol/L, a decrease in serum chloride levels was associated with an increased risk of mortality.These findings elucidate a marked nonlinear association between serum chloride levels and all-cause mortality in SICU patients, enhancing our comprehension of serum chloride's impact on clinical outcomes in this setting.

Keywords Serum chloride, ICU, Medical information mart for intensive care, All-cause mortality

*Correspondence:
Tianyu Lou
ltyxixi@126.com
Full list of author information is available at the end of the article

The SICU fulfills a critical role in modern healthcare systems, providing specialized care and monitoring for patients who have undergone surgery or sustained severe injuries [1]. Despite the high admission rates of surgical patients, SICUs in low- and middle-income countries continue to report elevated mortality rates [2, 3]. Therefore, identifying factors associated with poor outcomes in SICU patients is essential to reduce mortality rates.

Serum chloride is a key component of electrolyte balance in the human body [4]. Accounting for between 97 and 98% of all strong anion charges, and two-thirds of the negative charges in plasma, chloride is the dominant anion in the human body [5]. Its crucial roles include maintaining osmotic pressure, acid–base balance, and cellular homeostasis [6]. Variations in serum chloride levels, whether hypo- or hyperchloremia, significantly affect physiological function [7, 8]. The relationship between serum chloride levels and prognosis, as well as mortality in various diseases, has been extensively studied. Changes in serum chloride levels have been linked to negative outcomes in conditions such as congestive heart failure, renal diseases, hypertension, and sepsis [9–13]. However, most studies have focused on prognostic predictions for individual critical illnesses. The specific link between serum chloride levels and mortality in SICU patients remains poorly understood.

The aim of this study was to examine the relationship between serum chloride levels and mortality rates in SICU patients. To achieve this, we utilized data from the MIMIC-IV database to investigate the association between serum chloride concentrations and mortality at 30-day, 90-day, and 180-day intervals within this specific patient group.

Materials and methods

Study population

The objective of this retrospective analysis was to examine health-related data obtained from the MIMIC-IV (version 2.2) database. This database, a creation of the Computational Physiology Laboratory at the Massachusetts Institute of Technology, is maintained and developed by the same [14]. The data set includes records from 73,181 patients treated in the Intensive Care Unit (ICU) at Beth Israel Deaconess Medical Center, USA, from 2008 to 2019. As part of the publicly accessible MIMIC database, it contains only de-identified information to ensure patient anonymity. The development of the MIMIC-IV 2.2 database was approved by the Institutional Review Boards of both the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center. The principal investigator, Quan Ma, was granted authorization to use this database (Certification No.: 6413618). This study adheres to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology declaration for cross-sectional studies.

Inclusion criteria included: (1) Patients admitted to the SICU or trauma SICU(TSICU) for the first time; (2) Patients with first admission to the ICU and aged > =18 years. The exclusion criteria for this study were: (1) ICU stays lasting less than 24 h; (2) Absence of serum chloride indicators. The study sample comprised 10,996 patients. For details on the patient selection process, see Fig. 1.

Data extraction

For this study, data were extracted using Navicat Premium (version 16.2.11) and Structured Query Language (SQL) to retrieve records from the first day of ICU admission. Collected demographic data included age, gender, and weight. Comorbidities such as myocardial infarction,

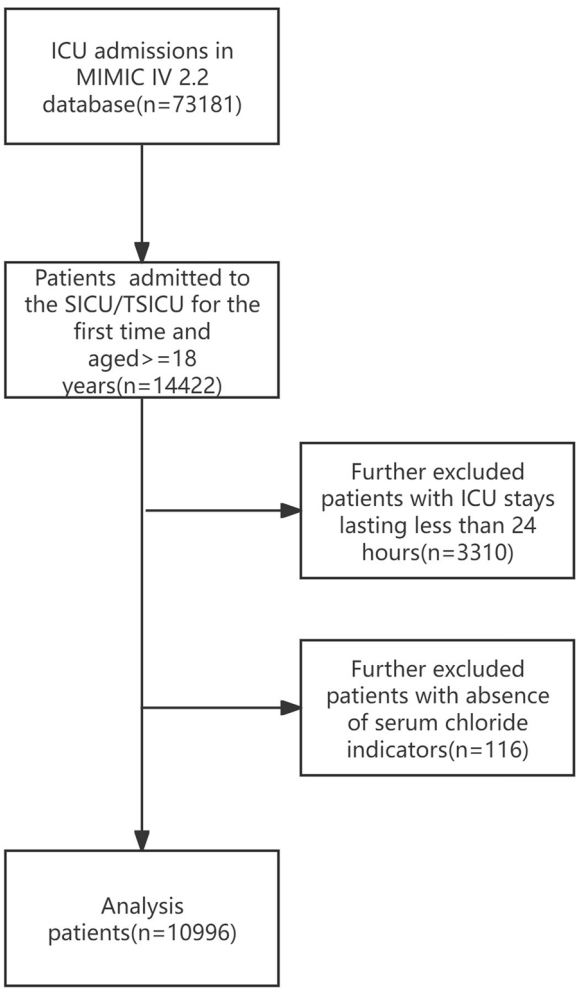

Fig. 1 Inclusion and exclusion criteria for study participants. ICU,Intensive Care Unit;SICU,Surgical Intensive Care Unit;TSICU,Trauma Surgical Intensive Care Unit

heart failure, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), liver disease, diabetes, renal disease, malignant cancer, and hypertension were investigated. Acute Kidney Injury (AKI) was examined as an acute complication. Disease severity was assessed using various scoring systems: the Acute Physiology Score III (APSIII) [15, 16], the Oxford Acute Severity of Illness Score (OASIS) [17], the Sequential Organ Failure Assessment (SOFA) [18], the Logistic Organ Dysfunction System (LODS) [19], and the Glasgow Coma Scale (GCS) [20]. Laboratory tests performed included measurements of white blood cells (WBC), red blood cells (RBC), platelets, chloride, calcium, potassium, sodium, glucose, prothrombin time (PT), blood urea nitrogen (BUN), and creatinine. Vital signs considered were systolic and diastolic blood pressure (SBP, DBP), heart rate, and temperature. The use of diuretics prior to SICU admission was recorded, including furosemide, torsemide, thiazides, amiloride, spironolactone, and mannitol. Implemented interventions included ventilator support and continuous renal replacement therapy (CRRT). Primary outcomes were defined by mortality rates at 30, 90, and 180 days post-admission. The K-Nearest Neighbors (KNN) algorithm was used for imputation of missing data for variables with less than 20% missing. Variables with 20–40% missing data were transformed into dummy variables. Variables with over 40% missing data were excluded from the study. For further details on missing data, see Supplementary Table 1.

Statistical analysis

Data processing and analysis were performed using R (version 4.4.0) and Zstats v1.0 (www.zstats.net). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are shown as median (interquartile range) [M (QL, QU)]. Categorical variables are summarized as counts and percentages. Continuous variables were analyzed using the Kruskal–Wallis rank sum test, and categorical variables were assessed using the chi-square test. Serum chloride levels were categorized into quartiles: Q1 (61–101 mmol/L), Q2 (101–104 mmol/L), Q3 (104–108 mmol/L), and Q4 (108–140 mmol/L). The relationship between serum chloride levels and 30-day, 90-day, and 180-day mortality was analyzed using Kaplan–Meier curves. Cox proportional hazards regression models were utilized for both univariate and multivariable analyses. Models were constructed to explore the association between serum chloride levels and mortality at 30 days, 90 days, and 180 days post-admission. Model 1 was unadjusted, Model 2 adjusted for demographic factors including gender, age, and weight; Model 3 additionally adjusted for laboratory indicators and comorbidities including glucose, WBC, RBC, platelet count, calcium, potassium, sodium, creatinine, BUN, PT, myocardial infarction, heart failure, cerebrovascular disease, COPD, liver disease, diabetes, renal disease, malignant cancer, hypertension, and AKI; Model 4 was adjusted for all variables. Serum chloride levels were included as a continuous variable, and restricted cubic spline (RCS) curves were plotted to analyze the dose–response relationship with mortality risk. Subgroup analysis was conducted to compare the relationship between serum chloride levels and overall mortality at 30, 90, and 180 days among SICU patients with different characteristics. For the subgroup analysis, the Benjamini–Hochberg correction was used for multiple comparisons. Statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics

This study encompassed 10,996 patients admitted to the SICU, with 54.43% ($n = 5984$) identified as male and 45.58% ($n = 5012$) as female. The median age was 63 years (IQR 51–76). Table 1 displays the baseline characteristics of the patients. Serum chloride levels were segmented into four quartiles: Q1 (61–101 mmol/L), Q2 (101–104 mmol/L), Q3 (104–108 mmol/L), and Q4 (108–140 mmol/L). The average ICU stay was 2.58 days, and the mean hospital stay was 8.25 days. The 30-day mortality rate post-admission was 12.78%, increasing to 17.14% at 90 days and 20.32% at 180 days. Lower serum chloride levels were linked with several factors, including advanced age, myocardial infarction, heart failure, COPD, liver disease, diabetes, renal disease, AKI, APS III, elevated heart rate, increased WBC count, reduced sodium levels, elevated BUN levels, higher PT levels, use of diuretics, receipt of CRRT, need for ventilator support, prolonged hospital LOS, and increased mortality rates at 30, 90, and 180 days ($p < 0.001$).

Clinical outcomes

Kaplan–Meier survival analysis curves were constructed to evaluate 30-day, 90-day, and 180-day mortality rates for patients in the SICU, grouping serum chloride levels into quartiles (Fig. 2). Marked differences in survival probabilities emerged among the four serum chloride quartiles throughout the 30-day, 90-day, and 180-day follow-up intervals ($P < 0.001$). Notably, within the 30-day observation period in the SICU, patients classified within the first quartile (Q1) showed the lowest survival probabilities, while those in the third quartile (Q3) exhibited the highest. This pattern persisted during the 90-day and 180-day follow-up periods.

Table 1 Characteristics and outcomes of participants categorized by serum chloride

Variables	Total (*n* = 10,996)	Q1 (*n* = 2365)	Q2 (*n* = 2305)	Q3 (*n* = 3509)	Q4 (*n* = 2817)	*P*
Age,years	63.00 (51.00, 76.00)	65.00 (53.00,77.00)	64.00 (52.00,77.00)	63.00 (50.00,75.00)	62.00 (48.00,75.00)	< 0.001
Male,n(%)	5984 (54.42)	1336 (56.49)	1301 (56.44)	1929 (54.97)	1418 (50.34)	< 0.001
Weight, kg	77.70 (65.20, 92.50)	78.00 (64.80,95.00)	78.50 (65.60,94.00)	78.50 (66.60,93.10)	75.50 (64.20,90.00)	< 0.001
Myocardial infarct, n(%)	855 (7.78)	225 (9.51)	185 (8.03)	245 (6.98)	200 (7.10)	0.002
Heart failure, n(%)	1435 (13.05)	476 (20.13)	322 (13.97)	372 (10.60)	265 (9.41)	< 0.001
Cerebrovascular disease, n(%)	2770 (25.19)	488 (20.63)	606 (26.29)	980 (27.93)	696 (24.71)	< 0.001
COPD, n(%)	2293 (20.85)	623 (26.34)	500 (21.69)	672 (19.15)	498 (17.68)	< 0.001
Liver disease, n(%)	1203 (10.94)	372 (15.73)	242 (10.50)	324 (9.23)	265 (9.41)	< 0.001
Diabetes, n(%)	2402 (21.84)	691 (29.22)	536 (23.25)	663 (18.89)	512 (18.18)	< 0.001
Renal disease, n(%)	1331 (12.10)	427 (18.05)	238 (10.33)	353 (10.06)	313 (11.11)	< 0.001
Malignant cancer, n(%)	1630 (14.82)	347 (14.67)	390 (16.92)	573 (16.33)	320 (11.36)	< 0.001
Hypertension, n(%)	4851 (44.12)	1106 (46.77)	1088 (47.20)	1536 (43.77)	1121 (39.79)	< 0.001
AKI, n(%)	7596 (69.08)	1757 (74.29)	1588 (68.89)	2325 (66.26)	1926 (68.37)	< 0.001
APS III	37.00 (28.00, 50.00)	42.00 (31.00,56.00)	36.00 (27.00,47.00)	35.00 (26.00,46.00)	38.00 (28.00,52.00)	< 0.001
OASIS	30.00 (25.00, 36.00)	31.00 (25.00,37.00)	29.00 (24.00,36.00)	29.00 (24.00,35.00)	31.00 (26.00,37.00)	< 0.001
SOFA	1.00 (0.00, 2.00)	1.00 (0.00,2.00)	1.00 (0.00,2.00)	1.00 (0.00,2.00)	1.00 (0.00,2.00)	< 0.001
LODS	3.00 (2.00, 5.00)	3.00 (2.00,6.00)	3.00 (2.00,5.00)	3.00 (2.00,5.00)	3.00 (2.00,5.00)	< 0.001
GCS	15.00 (15.00, 15.00)	15.00 (15.00,15.00)	15.00 (15.00,15.00)	15.00 (15.00,15.00)	15.00 (15.00,15.00)	< 0.001
Heart rate,beats/min	87.00 (74.00, 100.00)	90.00 (77.00,106.00)	87.00 (75.00,100.00)	85.00 (73.00,97.00)	86.00 (73.00,101.00)	< 0.001
SBP, mmHg	130.00 (113.00, 147.00)	131.00 (112.00,148.00)	132.00 (115.00,148.00)	130.00 (114.00,147.00)	126.00 (110.00,145.00)	< 0.001
DBP,mmHG	69.00 (59.00, 81.00)	70.00 (59.00,82.00)	70.00 (60.00,82.00)	69.00 (60.00,81.00)	68.00 (58.00,79.00)	< 0.001
Temperature, ℃	36.78 (36.44, 37.11)	36.83 (36.50,37.17)	36.83 (36.50,37.17)	36.72 (36.44,37.11)	36.67 (36.33,37.06)	< 0.001
Glucose, mg/dl	134.00 (111.00, 169.00)	136.00 (111.00,178.00)	138.00 (113.00,171.00)	132.00 (110.00,163.00)	133.00 (110.00,166.00)	< 0.001
WBC,10^9/L	11.00 (8.00, 14.90)	11.50 (8.20,15.90)	11.10 (8.30,15.00)	10.70 (7.90,14.30)	11.00 (7.80,14.80)	< 0.001
RBC,10^9/L	3.79 (3.28, 4.27)	3.71 (3.15,4.27)	3.92 (3.40,4.37)	3.86 (3.37,4.29)	3.65 (3.22,4.13)	< 0.001
Platelet, 10^9/L	208.00 (157.00, 269.00)	216.00 (157.00,285.00)	217.00 (166.00,277.00)	209.00 (160.00,266.00)	195.00 (147.00,252.00)	< 0.001
Calcium, mmol/L	8.40 (7.90, 8.90)	8.50 (8.10,9.00)	8.60 (8.10,9.00)	8.40 (8.00,8.80)	8.00 (7.50,8.53)	< 0.001
Potassium, mmol/L	4.10 (3.70, 4.50)	4.10 (3.70,4.60)	4.10 (3.80,4.50)	4.00 (3.70,4.40)	4.00 (3.70,4.40)	< 0.001
Sodium, mmol/L	139.00 (136.00, 141.00)	135.00 (132.00,137.00)	138.00 (136.00,140.00)	139.00 (138.00,141.00)	142.00 (140.00,144.00)	< 0.001
Creatinine, mg/dl	0.90 (0.70, 1.20)	0.90 (0.70,1.50)	0.90 (0.70,1.10)	0.90 (0.70,1.10)	0.90 (0.70,1.20)	< 0.001
BUN, mg/dl	16.00 (12.00, 24.00)	18.00 (12.00,30.00)	16.00 (12.00,23.00)	16.00 (11.00,22.00)	16.00 (11.00,24.00)	< 0.001
PT,sec	13.11 (12.10, 14.90)	13.49 (12.20,15.70)	13.00 (12.10,14.60)	12.94 (12.03,14.50)	13.36 (12.20,15.10)	< 0.001
Diuretics,n(%)	749 (6.81)	304 (12.85)	162 (7.03)	173 (4.93)	110 (3.90)	< 0.001
Ventilator, n(%)	8891 (80.86)	1958 (82.79)	1821 (79.00)	2782 (79.28)	2330 (82.71)	< 0.001
CRRT, n(%)	310 (2.82)	144 (6.09)	52 (2.26)	60 (1.71)	54 (1.92)	< 0.001
Hospital LOS, days	8.25 (4.93, 14.61)	9.22 (5.53,16.41)	7.96 (4.89,13.54)	7.75 (4.67,13.52)	8.46 (4.85,15.05)	< 0.001
ICU LOS, days	2.58 (1.65, 4.99)	2.76 (1.69,5.12)	2.50 (1.64,4.76)	2.29 (1.55,4.69)	2.77 (1.72,5.78)	< 0.001
30 Day death, n(%)	1405 (12.78)	405 (17.12)	270 (11.71)	367 (10.46)	363 (12.89)	< 0.001
90 Day death, n(%)	1885 (17.14)	539 (22.79)	367 (15.92)	503 (14.33)	476 (16.90)	< 0.001
180 Day death, n(%)	2234 (20.32)	630 (26.64)	441 (19.13)	618 (17.61)	545 (19.35)	< 0.001

Continuous variables are presented as medians (interquartile ranges), while categorical variables are reported as numbers (percentages). Statistical analyses included the Kruskal–Wallis test for continuous variables and the Chi-square test for categorical variables

Q1 61–101 mmol/L, *Q2* 101–104 mmol/L, *Q3* 104–108 mmol/L, *Q4* 108–140 mmol/L, *AKI* Acute Kidney Injury, *SOFA* Sequential Organ Failure Assessment, *APS* Acute Physiology Score, *OASIS* Oxford Acute Severity of Illness Score, *LODS* Lactate-Oxygenation-Derived Severity Score, *GCS* Glasgow Coma Scale, *COPD* Chronic Obstructive Pulmonary Disease, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *WBC* White Blood Cell, *RBC* Red Blood Cell, *BUN* Blood Urea Nitrogen, *PT* Prothrombin Time, *CRRT* Continuous Renal Replacement Therapy, *LOS* Length of Stay, *ICU* Intensive Care Unit

Employing the Cox proportional hazards model, an extensive evaluation was undertaken to assess the link between serum chloride levels and all-cause mortality among patients admitted to the SICU (Table 2). Model 4 indicated that, after adjustment for all covariates, serum chloride, analyzed as a continuous variable, was significantly associated with mortality at 30-day (HR = 0.96, 95%CI: 0.95–0.97, $p < 0.001$), 90-day

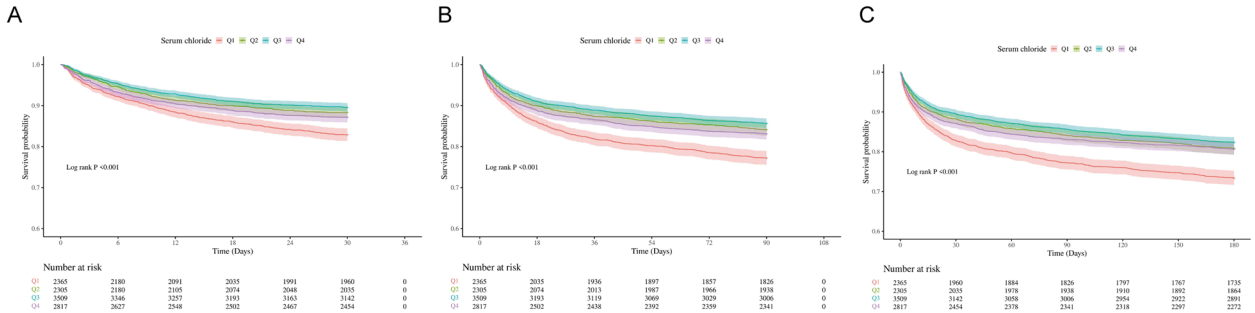

Fig. 2 Kaplan–Meier survival analysis curves. For (**A**) 30-day, (**B**) 90-day, and (**C**) 180-day all-cause mortality

Table 2 Cox proportional hazard ratios for 30-day, 90-day and 180-day all-cause mortality

Variables	Model 1		Model 2		Model 3		Model 4	
	HR(95% CI)	*P*-values	HR(95% CI)	*P*-values	HR(95% CI)	*P*-values	HR(95% CI)	*P*-values
30 days mortality								
Serum Chloride(continuous)	0.98 (0.97 ~ 0.99)	< 0.001	0.99 (0.98 ~ 0.99)	0.043	0.97 (0.96 ~ 0.98)	< 0.001	0.96 (0.95 ~ 0.97)	< 0.001
Serum Chloride(categorical)								
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.67 (0.57 ~ 0.78)	< 0.001	0.75 (0.64 ~ 0.87)	< 0.001	0.73 (0.62 ~ 0.86)	< 0.001	0.76 (0.64 ~ 0.89)	0.001
Q3	0.59 (0.51 ~ 0.68)	< 0.001	0.71 (0.61 ~ 0.82)	< 0.001	0.67 (0.57 ~ 0.79)	< 0.001	0.68 (0.58 ~ 0.80)	< 0.001
Q4	0.74 (0.64 ~ 0.85)	< 0.001	0.89 (0.77 ~ 1.03)	0.117	0.75 (0.61 ~ 0.91)	0.004	0.65 (0.53 ~ 0.79)	< 0.001
P for trend		< 0.001		0.063		0.002		< 0.001
90 days mortality								
Serum Chloride(continuous)	0.98 (0.97 ~ 0.99)	< 0.001	0.99 (0.98 ~ 0.99)	0.037	0.98 (0.97 ~ 0.99)	0.002	0.97 (0.96 ~ 0.98)	< 0.001
Serum Chloride(categorical)								
Q1	1.00 (Reference		1.00 (Reference		1.00 (Reference		1.00 (Reference	
Q2	0.67 (0.59 ~ 0.77)	< 0.001	0.75 (0.66 ~ 0.86)	< 0.001	0.76 (0.65 ~ 0.87)	< 0.001	0.78 (0.68 ~ 0.90)	< 0.001
Q3	0.60 (0.53 ~ 0.68)	< 0.001	0.72 (0.64 ~ 0.82)	< 0.001	0.71 (0.62 ~ 0.82)	< 0.001	0.72 (0.62 ~ 0.83)	< 0.001
Q4	0.72 (0.64 ~ 0.82)	< 0.001	0.88 (0.78 ~ 1.00)	0.058	0.80 (0.67 ~ 0.95)	0.011	0.71 (0.59 ~ 0.84)	< 0.001
P for trend		< 0.001		0.031		0.007		< 0.001
180 days mortality								
Serum Chloride(continuous)	0.98 (0.97 ~ 0.98)	< 0.001	0.99 (0.98 ~ 0.99)	0.011	0.98 (0.97 ~ 0.99)	< 0.001	0.97 (0.96 ~ 0.98)	< 0.001
Serum Chloride(categorical)								
Q1	1.00 (Reference		1.00 (Reference		1.00 (Reference		1.00 (Reference	
Q2	0.69 (0.61 ~ 0.77)	< 0.001	0.76 (0.67 ~ 0.86)	< 0.001	0.76 (0.66 ~ 0.86)	< 0.001	0.78 (0.68 ~ 0.89)	< 0.001
Q3	0.62 (0.56 ~ 0.70)	< 0.001	0.75 (0.66 ~ 0.84)	< 0.001	0.73 (0.64 ~ 0.83)	< 0.001	0.73 (0.64 ~ 0.84)	< 0.001
Q4	0.70 (0.62 ~ 0.79)	< 0.001	0.86 (0.76 ~ 0.97)	0.012	0.77 (0.66 ~ 0.91)	0.002	0.69 (0.59 ~ 0.81)	< 0.001
P for trend		< 0.001		0.008		0.001		< 0.001

Model 1: Crude

Model 2: Adjust: Gender, Age, Weight

Model 3: Adjust: Gender, Age, Weight, Glucose, WBC, RBC, Platelet, Calcium, Potassium, Sodium, Creatinine, BUN, PT, Myocardial infarct, Heart failure, Cerebrovascular disease, COPD, Liver disease, Diabetes, Renal disease, Malignant cancer, Hypertension, AKI

Model 4: Adjust: Gender, Age, Weight, APSIII, OASIS, SOFA, LODS, GCS, Heart rate, SBP, DBP, Temperature, Glucose, WBC, RBC, Platelet, Calcium, Potassium, Sodium, Creatinine, BUN, PT, Myocardial infarct, Heart failure, Cerebrovascular disease, COPD, Liver disease, Diabetes, Renal disease, Malignant cancer, Hypertension, AKI, Diuretics,Ventilator, CRRT

HR Hazard Ratio, *CI* Confidence Interval, *AKI* Acute Kidney Injury, *SOFA* Sequential Organ Failure Assessment, *APS* Acute Physiology Score, *OASIS* Oxford Acute Severity of Illness Score, *LODS* Lactate-Oxygenation-Derived Severity Score, *GCS* Glasgow Coma Scale, *COPD* Chronic Obstructive Pulmonary Disease, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *WBC* White Blood Cell, *RBC* Red Blood Cell, *BUN* Blood Urea Nitrogen, *PT* Prothrombin Time, *CRRT* Continuous Renal Replacement Therapy, *LOS* Length of Stay, *ICU* Intensive Care Unit

(HR = 0.97, 95%CI: 0.96–0.98, $p < 0.001$), and 180-day (HR = 0.97, 95%CI: 0.96–0.98, $p < 0.001$) intervals. Even after serum chloride levels were divided into four groups, notable statistical differences persisted in mortality rates at 30-day, 90-day, and 180-day intervals among these groups in Model 4 ($p < 0.001$) (Table 2).

To probe the potential non-linear connection between serum chloride levels and clinical outcomes, the restricted cubic spline (RCS) model was utilized (Fig. 3). Following adjustment for all covariates, RCS curve analysis revealed a non-linear inverse relationship between serum chloride concentrations and mortality risks at 30 days, 90 days, and 180 days, with *P*-values for non-linearity recorded at 0.032, 0.002, and 0.002, respectively. Moreover, it was observed that below a concentration of 104 mmol/L, a reduction in serum chloride levels was linked with an elevated risk of mortality.

Subgroup analysis

In this study, subgroup analyses were conducted on SICU patients differentiated by age, gender, myocardial infarct, cerebrovascular disease, COPD, liver disease, diabetes, malignant cancer, and hypertension to investigate the link between serum chloride levels and all-cause mortality (Table 3). Results demonstrated a significant negative association between serum chloride levels and all-cause mortality across specific subgroups: age < 63 (HR: 0.63, 95%CI: 0.51–0.77, $p < 0.001$), female (HR: 0.68, 95%CI: 0.58–0.78, $p < 0.001$), absence of diabetes (HR: 0.74, 95%CI: 0.66–0.83, $p < 0.001$), and absence of hypertension (HR: 0.68, 95%CI: 0.59–0.79, $p < 0.001$). Further analyses indicated that the negative association between serum chloride levels and mortality was consistent regardless of the presence of myocardial infarct (YES: HR 0.72, 95% CI: 0.53–0.96, $p = 0.035$ vs. NO: HR 0.81, 95%CI: 0.72–0.90, $p < 0.001$), cerebrovascular disease (YES: HR 0.82, 95%CI: 0.69–0.97, $p = 0.030$ vs. NO: HR 0.73, 95% CI: 0.64–0.84, $p < 0.001$), COPD (YES: HR 0.77, 95%CI: 0.62–0.96, $p = 0.031$ vs. NO: HR 0.80, 95%CI: 0.71–0.90, $p < 0.001$), liver disease (YES: HR 0.59, 95%CI: 0.46–0.77, $p < 0.001$ vs. NO: HR 0.86, 95%CI: 0.76–0.96, $p < 0.017$), or malignant cancer (YES: HR 0.74, 95%CI: 0.57–0.96, $p = 0.031$ vs. NO: HR 0.80, 95% CI: 0.71–0.90, $p < 0.001$). These patterns persisted across mortality assessments at 90-day and 180-day intervals. Moreover, significant interactions were identified within age and gender groups concerning 30-day, 90-day, and 180-day mortality outcomes.

Discussion

In this retrospective observational study of SICU patients, we explored for the first time the relationship between serum chloride levels and mortality rates at 30, 90, and 180 days. Our findings indicate that, after controlling for all confounding variables, serum chloride levels were inversely associated with overall mortality in this group. Additionally, this inverse association manifested an L-shaped pattern, suggesting that below a threshold of 104 mmol/L, a reduction in serum chloride levels was associated with an increased mortality risk. Subgroup analyses confirmed this negative association across various patient subgroups within the SICU population, providing important insights into the potential role of serum chloride levels in predicting patient outcomes in SICU.

Serum chloride plays a crucial role in maintaining acid–base balance, regulating osmotic pressure, and supporting cellular function within the body [21, 22]. Alongside sodium, chloride is essential for the maintenance of extracellular fluid volume and cellular membrane potential [23]. It affects several organ systems: in the renal system, chloride is responsible for regulating tubular reabsorption and secretion, essential for maintaining electrolyte balance and renal function integrity [24]; in the cardiovascular system, it influences myocardial excitability and vascular tone, affecting cardiac performance and blood pressure control [25]; in the neurological system, disturbances in chloride levels can lead to neurological symptoms such as confusion and seizures [26]. Thus, variations in serum chloride levels are often associated with certain comorbidities, including heart failure [27], renal disease [28], and hypertension [29]. Moreover, management practices for pre-existing conditions, such as the use of diuretics, can reduce serum chloride concentrations [30]. Consequently, serum chloride levels may act as indicators of underlying pathological conditions, the presence of comorbidities, and diuretic use. Therefore, this study included consideration of these potential influencing factors and made adjustments for them in applying the Cox proportional hazards model and the RCS model.

The relationship between serum chloride levels and patient prognosis and mortality rates is complex and influenced by multiple factors. Extensive research has demonstrated a link between reduced serum chloride levels and increased mortality across varied populations. Serum chloride is an independent predictor of mortality in hypertensive patients, with lower levels associating with increased mortality in this group [29]. Additionally, a study using the MIMIC database explored the U-shaped relationship between serum chloride levels and in-hospital mortality among ICU patients with congestive heart failure [10]. A

Table 3 Subgroup analysis of the relationship between serum chloride and 30-day, 90-day, 180-day mortality

Variables	30-day mortality			90-day mortality			180-day mortality		
	HR (95%CI)	*P*	P for interaction	HR (95%CI)	*P*	P for interaction	HR (95%CI)	*P*	P for interaction
All patients	0.79 (0.71 ~ 0.87)	< 0.001		0.78 (0.71 ~ 0.86)	< 0.001		0.78 (0.72 ~ 0.85)	< 0.001	
Age			0.013			0.009			0.004
< 63	0.63 (0.51 ~ 0.77)	< 0.001		0.65 (0.54 ~ 0.77)	< 0.001		0.65 (0.56 ~ 0.77)	< 0.001	
> = 63	0.91 (0.80 ~ 1.02)	0.132		0.89 (0.80 ~ 0.99)	0.042		0.89 (0.81 ~ 0.98)	0.020	
Gender			0.018			0.009			0.004
Female	0.68 (0.58 ~ 0.78)	< 0.001		0.67 (0.59 ~ 0.77)	< 0.001		0.67 (0.59 ~ 0.76)	< 0.001	
Male	0.90 (0.78 ~ 1.05)	0.198		0.89 (0.78 ~ 1.01)	0.077		0.89 (0.80 ~ 1.00)	0.060	
Myocardial infarct			0.612			0.916			0.844
No	0.81 (0.72 ~ 0.90)	< 0.001		0.79 (0.72 ~ 0.87)	< 0.001		0.79 (0.72 ~ 0.86)	< 0.001	
Yes	0.72 (0.53 ~ 0.96)	0.035		0.77 (0.60 ~ 1.00)	0.059		0.77 (0.61 ~ 0.98)	0.040	
Cerebrovascular disease			0.501			0.612			0.763
No	0.73 (0.64 ~ 0.84)	< 0.001		0.74 (0.66 ~ 0.83)	< 0.001		0.75 (0.68 ~ 0.83)	< 0.001	
Yes	0.82 (0.69 ~ 0.97)	0.030		0.81 (0.69 ~ 0.94)	0.008		0.80 (0.69 ~ 0.92)	0.003	
COPD			0.811			0.916			0.844
No	0.80 (0.71 ~ 0.90)	< 0.001		0.79 (0.71 ~ 0.88)	< 0.001		0.80 (0.73 ~ 0.88)	< 0.001	
Yes	0.77 (0.62 ~ 0.96)	0.031		0.80 (0.66 ~ 0.96)	0.019		0.77 (0.65 ~ 0.91)	0.003	
Liver disease			0.022			0.059			0.050
No	0.86 (0.76 ~ 0.96)	0.017		0.83 (0.75 ~ 0.92)	< 0.001		0.83 (0.76 ~ 0.91)	< 0.001	
Yes	0.59 (0.46 ~ 0.77)	< 0.001		0.64 (0.51 ~ 0.80)	< 0.001		0.64 (0.52 ~ 0.79)	< 0.001	
Diabetes			0.029			0.054			0.050
No	0.74 (0.66 ~ 0.83)	< 0.001		0.74 (0.67 ~ 0.82)	< 0.001		0.75 (0.68 ~ 0.82)	< 0.001	
Yes	1.00 (0.81 ~ 1.23)	0.980		0.96 (0.80 ~ 1.15)	0.642		0.94 (0.79 ~ 1.11)	0.446	
Malignant cancer			0.684			0.845			0.844
No	0.80 (0.71 ~ 0.90)	< 0.001		0.80 (0.72 ~ 0.88)	< 0.001		0.79 (0.72 ~ 0.86)	< 0.001	
Yes	0.74 (0.57 ~ 0.96)	0.031		0.75 (0.61 ~ 0.92)	0.009		0.79 (0.66 ~ 0.95)	0.015	
Hypertension			0.013			0.058			0.018
No	0.68 (0.59 ~ 0.79)	< 0.001		0.71 (0.63 ~ 0.81)	< 0.001		0.71 (0.63 ~ 0.79)	< 0.001	
Yes	0.94 (0.81 ~ 1.09)	0.435		0.88 (0.77 ~ 1.00)	0.060		0.89 (0.79 ~ 1.00)	0.063	

HR Hazard Ratio, *CI* Confidence Interval, *COPD* Chronic Obstructive Pulmonary Disease

The *p*-values were adjusted for multiple comparisons using the Benjamini–Hochberg correction

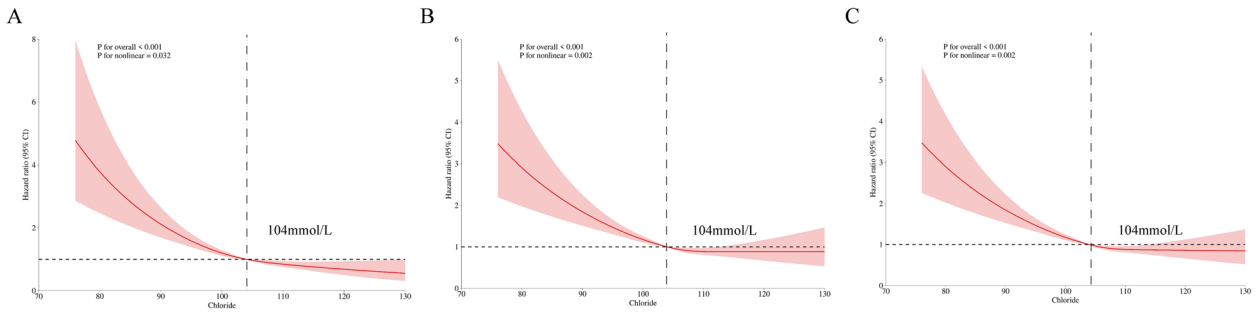

Fig. 3 Restricted cubic spline curve. Illustrating the hazard ratio for serum chloride after adjusting for Gender, Age, Weight, APSIII, OASIS, SOFA, LODS, GCS, Heart rate, SBP, DBP, Temperature, Glucose, WBC, RBC, Platelet, Calcium, Potassium, Sodium, Creatinine, BUN, PT, Myocardial infarct, Heart failure, Cerebrovascular disease, COPD, Liver disease, Diabetes, Renal disease, Malignant cancer, Hypertension, AKI, Diuretics,Ventilator, CRRT. **A** 30-day mortality, **B** 90-day mortality, **C** 180-day mortality

retrospective cohort study revealed an L-shaped association between serum chloride levels and both 90-day and 365-day all-cause mortality in ICU patients with COPD [9]. Similarly, another retrospective study on critically ill patients undergoing CRRT showed that hypochloremia, both prior to and during treatment, was associated with significantly higher 90-day mortality [31]. In surgical and trauma patients, variations in serum chloride levels have been associated with poor outcomes, including higher mortality rates. Fluctuations in serum chloride levels have also been connected to increased 90-day mortality in patients undergoing non-cardiac surgery [32]. This research further revealed that the preoperative hypochloremia group was 1.83 times more likely to develop acute kidney injury than the group with normal serum chloride levels [32]. Moreover, another study reported that hypochloremia occurring within 48 h post-surgery was independently associated with an increased risk of in-hospital mortality among postoperative critically ill patients, highlighting its potential role as a prognostic indicator [33]. Consistent with earlier findings, our study also identifies a negative association between serum chloride levels and all-cause mortality in SICU patients. Interestingly, this association diminishes when serum chloride concentrations exceed 104 mmol/L.

In addition, given the distinct characteristics of various patient groups, subgroup analyses were conducted. The results suggested that most variables had little impact on the relationship between serum chloride levels and overall mortality in SICU patients, highlighting the robustness and pertinence of our findings. Significant interactions were also observed involving age and gender groups regarding 30-day, 90-day, and 180-day mortality outcomes. Specifically, compared to patients aged > = 63, those aged < 63 showed a more pronounced inverse association between serum chloride levels and mortality rates in the SICU. Similarly, among female patients, the negative association between serum chloride levels and mortality rates was more marked.

While our study sheds light on the association between serum chloride levels and mortality rates in SICU patients using a substantial dataset from the MIMIC-IV database, it is constrained by several limitations. Firstly, the study's single-center, retrospective nature and its reliance on the MIMIC-IV database alone may restrict the broader applicability of the findings. Future studies should incorporate data from multiple centers or employ prospective designs to broaden the relevance and utility of the research. Secondly, despite the use of various models to adjust for confounders, unidentified or unmeasured variables related to serum chloride levels or mortality rates may still exist, necessitating cautious interpretation of our findings. Lastly, while an association between serum chloride levels and mortality rates in SICU patients was noted, establishing causality is complex, and additional studies are required to elucidate the underlying mechanisms and causal pathways.

Conclusion

Our study demonstrates an L-shaped association between serum chloride levels and all-cause mortality at 30-day, 90-day, and 180-day intervals in SICU patients. Further research is necessary to examine the relationship between serum chloride levels and outcomes in patients admitted to trauma/surgical ICUs, as well as the potential benefits of various chloride-monitoring strategies or interventions aimed at adjusting serum chloride levels.

Abbreviations

ICU	Intensive Care Unit
SICU	Surgical Intensive Care Unit
TSICU	Trauma Surgical Intensive Care Unit
MIMIC-IV	Medical Information Mart for Intensive Care IV
RCS	Restricted Cubic Spline
HR	Hazard Ratio
CI	Confidence Interval

SQL	Structured Query Language
AKI	Acute Kidney Injury
SOFA	Sequential Organ Failure Assessment
APS	Acute Physiology Score
OASIS	Oxford Acute Severity of Illness Score
LODS	Lactate-Oxygenation-Derived Severity Score
GCS	Glasgow Coma Scale
COPD	Chronic Obstructive Pulmonary Disease
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
WBC	White Blood Cell
RBC	Red Blood Cell
BUN	Blood Urea Nitrogen
PT	Prothrombin Time
CRRT	Continuous Renal Replacement Therapy
LOS	Length of Stay
KNN	K-Nearest Neighbors

Supplementary Information

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Supplementary Material 1.

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Author's contributions
QM and BX contributed to the conception and design of the study. QM, WT, and KW conducted the data analysis and interpretation. QM prepared the initial draft of the manuscript. TL performed a critical review, made revisions, and gave final approval of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability
In this study, publicly accessible datasets were analyzed. These datasets can be accessed at the following link: https://physionet.org/content/mimiciv/2.2/. Additionally, the datasets utilized and analyzed during the course of this research are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The database utilized in this study received approval for research use from the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, with a waiver of informed consent granted for studies using the database. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Urology, Shaoxing Central Hospital, Shaoxing, Zhejiang 312030, China. [2]Department of Intensive Care Unit, Shaoxing Central Hospital, Shaoxing, Zhejiang 312030, China. [3]Department of General Medicine, Shaoxing Central Hospital, Shaoxing, Zhejiang 312030, China.

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